72. The antibody or antigen binding fragment of Claim 71 wherein the antibody or antigen binding fragment can compete with monoclonal antibody 7B11 for binding to said human C-C chemokine receptor 3 protein.

73. An antibody or antigen binding fragment thereof having specificity for a naturally-occurring human C-C chemokine receptor 3 protein, wherein the antibody or antigen binding fragment can compete with monoclonal antibody 7B11 for binding to said human C-C chemokine receptor 3 protein.

74. A hybridoma which produces the antibody of Claim 73.

REMARKS

Amendment to the Title

The title of the application has been amended to more clearly indicate and describe the claimed invention as suggested by the Examiner.

Amendments to the Specification

The Specification has been amended to correct a typographical error and to insert the current address for the American Type Culture Collection. No new matter is added by these amendments.

Claim Amendments

Claims 38, 39, 49-51, 53 and 55 have been amended to recite antigen binding fragments. Support for this amendment can be found throughout the Specification, for example, at page 38, lines 10-13 and 23-27.

Claims 38, 49 and 53 have also been amended to recite a "naturally-occurring" mammalian C-C chemokine receptor 3 protein. Support for this amendment can be found throughout the Specification, for example, at page 30, line 11.

Claim 38 has been amended to recite an antibody or antigen binding fragment which "specifically" binds to a naturally-occurring mammalian C-C chemokine receptor 3 protein. Support for this amendment can be found throughout the Specification, for example, at page 35, lines 28-30.

Claim 49 has also been amended to replace "blocks" with "inhibits". Support for this amendment can be found throughout the Specification, for example, at page 35, line 30, through page 36, line 9.

New Claims 68-69 have been added which are drawn to the hybridoma cell line deposited as ATCC Accession No. HB-12195 and to antibodies produced by this hybridoma cell line, respectively. Support for these claims can be found at page 17, lines 19-25, for example.

New Claims 70-74 have also been added. These claims are based on former Claims 38, 49, 50, 53, and 57, respectively. Support for these claims can be found throughout the Specification, for example, at page 36, lines 10-19.

No new matter is added by these amendments.

Corrected Filing Receipt

Applicants note that the word "Receptor" has been omitted in the title in the Official Filing Receipt received on June 10, 1998. A copy of the Filing Receipt with the correction noted in red is enclosed herewith. Applicants respectfully request correction of this error and issuance of a Corrected Filing Receipt.

Objection to the Disclosure

The Examiner has objected to the disclosure because the disclosure contains reference to the former address for the American Type Culture Collection (ATCC). The Specification has been amended to update the address for the ATCC as required by the Examiner.

Rejection of Claim 58 Under 35 U.S.C. §112, First Paragraph

Claim 58 is rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. The Examiner states that the hybridoma cell line recited in Claim 58 is essential to the claimed invention, and that the reproduction of antibodies from the disclosed hybridoma is an extremely unpredictable event. The Examiner further states that the hybridoma 7B11, disclosed on page 17, lines 22-25, of the specification must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. The Examiner states that the instant specification does not disclose a repeatable process to obtain the hybridomas and it is not apparent if the hybridomas are readily available to the public. The

Examiner sets forth at pages 3-4 of the pending Office Action requirements relating to biological deposits under the Budapest Treaty.

The 7B11 hybridoma cell line was deposited on September 25, 1996, at the American Type Culture Collection under the terms of the Budapest Treaty. The deposit date, name and address of the depository are referenced at page 17, lines 21-25, and the Accession Number was inseted by Preliminary Amendment on November 3, 1997. A Declaration Under 37 C.F.R. §1.806 and §1.808 is submitted concurrently herewith, and Applicants believe that all of the requirements relating to this biological deposit have been satisfied, obviating the rejection. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 49 and 53 Under 35 U.S.C. §112, First Paragraph

Claims 49 and 53 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention at the time the application was filed. The Examiner states that the specification discloses that the antibodies of the present invention have specificity for human CKR3 and have an epitopic specificity similar to that of murine 7B11 monoclonal antibody. The Examiner further states that the specification teaches only the antibodies to human CKR3 (e.g., pages 59-77) but does not teach antibodies (other than the monoclonal antibodies disclosed) to any other mammalian receptor. The Examiner states that the specification does not disclose the amino acid sequences for e.g., ovine, bovine, porcine, equine, feline, etc., CKR3. The Examiner states that the description of mammalian CKR3 receptors is limited to their function, and to a method for isolating the claimed sequence from its natural source. Thus, the Examiner concludes that at the time the application was filed, antibodies to mammalian CKR3 were not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention.

Applicants respectfully traverse this rejection. The Specification (for example page 28, line 25, through page 29, line 15) discloses that the approaches described in the application for isolation and manipulation of the genomic and cDNAs of human CCR3, for construction of vectors and host strains and for production and use of the receptor and fragments thereof can be applied to other mammalian species. For example, the specific human CCR3 cDNA or genomic clones, or portions thereof, can be used as probes to detect and/or recover homologous CCR3

genes from other mammalian species such as primates, bovine, ovine, equine, canine, feline, and rodent species, using art recognized techniques. The methods described in the application (e.g., pages 35-42 and Examples 5 and 6) for the production of polyclonal and monoclonal antibodies can be applied to non-human mammalian CCR3 proteins to produce anti-CCR3 antibodies which bind to (e.g., are specific for) non-human mammalian CCR3. The written description requirement of 35 U.S.C. §112 is intended to require applicants to describe their invention with enough specificity so that it is clear that applicants invented the subject matter which is claimed and that applicants intended the claimed subject matter to be part of the invention (see, for example, 1212 TMOG 16 (1998)). Applicants believe that these requirements are met in the instant application.

For these reasons, Applicants believe the subject matter of Claims 49 and 53 was described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention at the time the application was filed. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 38-39 and 49-58 Under 35 U.S.C. §112, First Paragraph

Claims 38-39 and 49-58 are rejected under 35 U.S.C. §112, first paragraph, because the Examiner states that the specification does not enable a person skilled in the art to make and use the invention commensurate in scope with the claims. The Examiner states that the specification, while being enabling for an antibody which binds to a human chemokine receptor 3 protein comprising the amino acid sequence of SEQ ID NO: 4, does not reasonably provide enablement for "all" antibodies or functional portions thereof which bind to a mammalian chemokine receptor 3 protein or portion of said receptor protein. The Examiner states that the claimed invention broadly encompasses all antibodies or functional portions thereof which bind to a mammalian chemokine receptor 3 protein or portion of said receptor protein. The Examiner further states that while the specification discloses that the antibodies of the present invention have specificity for human CKR3 and that this is the biological property which the antibodies are expected to exhibit, the specification is non-enabling for the unlimited number of antibodies which are encompassed by the scope of the claims in the absence of structural limitations regarding human CKR3 recited in the claims.

Claims 38, 49 and 53 have been amended to refer to "naturally-occurring" mammalian

C-C chemokine receptor 3 protein and to delete the reference to portions of the receptor. The Specification is clearly enabling for antibodies reactive with these proteins for the reasons discussed in the response to the rejection of Claims 49 and 53 under 35 U.S.C. §112, first paragraph, above.

Thus, Applicants believe that the claimed invention is fully enabled by the Specification. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 38 and 39 Under 35 U.S.C. §112, Second Paragraph

Claims 38 and 39 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The Examiner states that Claim 38, line 1, is vague and indefinite because it is unclear from the recitation of "functional portion thereof" which function Applicants intend to claim. Claim 39 is rejected as vague and indefinite insofar as it depends on Claim 38 for this limitation.

Claim 38 has been amended to replace "functional portion" with "antigen binding fragment", specifying a function as suggested by the Examiner. The Specification describes in detail examples of antigen binding fragments which are included within the scope of the invention, and provides guidance regarding the preparation of such fragments. At page 38, line 23, through page 39, line 2, the Specification states:

> For example, antibody fragments capable of binding to a mammalian CKR-3 receptor or portion thereof, including, but not limited to, Fv, Fab, Fab' and $F(ab')_2$ fragments are encompassed by the invention. Such fragments can be produced by enzymatic cleavage or by recombinant techniques. For instance, papain or pepsin cleavage can generate Fab or $F(ab')_2$ fragments, respectively. Antibodies can also be produced in a variety of truncated forms using antibody genes in which one or more stop codons has been introduced upstream of the natural stop site. For example, a chimeric gene encoding a $F(ab')_2$ heavy chain portion can be designed to include DNA sequences encoding the CH_1 domain and hinge region of the heavy chain.

The Specification, at pages 47-50, details binding assays which can be used to assess the ability of a specified fragment to bind CCR3.

The Specification is required to contain one or more claims which particularly point out and distinctly claim the subject matter which Applicants regard as the invention. However, the claims are read in light of the teachings of the Specification, and these teachings must be

considered when determining claim "definiteness". In re Moore, 439 F.2d 1232, 169 USPQ 236 (CCPA 1971); Ex parte Balzarini, 21 USPQ 2d 1892, 1899 (Bd. App. 1991).

The underlying and essential query with respect to definiteness of the claims is whether one of ordinary skill in the art would have difficulty ascertaining the metes and bounds of the claims as presented. Ex parte Balzarini, 21 USPQ 2d 1892, 1898 (Bd. App. 1991). In the present application, it is clear that the ordinarily skilled artisan would not have trouble determining the metes and bounds of the claimed invention, as the Specification provides clear guidelines and definitions of the terms of the claims. Given the guidance and exemplification in the Specification, the claimed invention particularly points out and distinctly claims the subject matter which Applicants regard as the invention. Reconsideration and withdrawal of the rejection are respectfully requested.

Provisional Double Patenting Rejection of Claims 49-52 Under 35 U.S.C. §101

Claims 49-52 are provisionally rejected under 35 U.S.C. §101 as being substantial duplicates of Claims 53-56, respectively. The Examiner states that when two claims in an application are duplicates, or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to reject the other as being a substantial duplicate of the allowed claim.

Applicants respectfully traverse this rejection. It is believed that 35 U.S.C. §101 proscribes claiming the same subject matter in two different patents, and rejection under 35 U.S.C. §101 is improper under the present circumstances. Duplicate claims, if present, are ordinarily objected to under 37 C.F.R. §1.75 (MPEP §706.03(k)). "However, court decisions have confirmed applicant's right to restate (i.e., by plural claiming) the invention in a reasonable number of ways. Indeed, a mere difference in scope between claims has been held to be enough" (MPEP §706.03(k)). In this case, Claim 49, and claims dependent thereon, is not coextensive with Claim 53 and claims dependent thereon. Claim 49 and claims dependent thereon are drawn to an antibody or antigen binding fragment thereof having specificity for mammalian CCR3 or portion thereof, which inhibits binding of a ligand to the receptor and inhibits function associated with binding of the ligand to the receptor. Claim 53 and claims dependent thereon are drawn to an antibody or antigen binding fragment thereof having binding specificity for mammalian CCR3 or portion thereof, which can compete with monoclonal antibody 7B11 for binding to human CCR3 or portion thereof. The ability of an antibody or antigen binding fragment thereof

to inhibit binding of a ligand to the receptor and inhibit function associated with binding of the ligand to the receptor is not necessarily coextensive with the ability to compete with monoclonal antibody 7B11 for binding to human CCR3 or portion thereof. Thus, Claims 49-52 and 53-56 are not duplicates or essential duplicates of each other. Reconsideration and withdrawal of the provisional rejection are respectfully requested.

Rejection of Claims 38-39 and 49-50 Under 35 U.S.C. §103

Claims 38-39 and 49-50 are rejected under 35 U.S.C. §103 as being unpatentable over Yamagami *et al.* (*Biochem. Biophy Res. Comm. 202*(2):1156-1162 (1994); Reference W) in view of Lerner (*Nature 299*:592-596 (1982); Reference V) and Harlow *et al.* (Antibodies: A Laboratory Manual, Chapter 5, page 76, Cold Spring Harbor Laboratory (1988); Reference U). The Examiner states that Yamagami *et al.* disclose the cDNA cloning of a human monocyte chemoattractant protein 1 receptor which has a stretch of 10 amino acids identical with the amino acid sequence depicted in SEQ ID NO: 2 of the present application. The Examiner further states that these residues are not part of the transmembrane domain. The Examiner states that Yamagami *et al.* fail to disclose antibodies to the human monocyte chemoattractant protein 1 receptor.

The Examiner further states that Lerner teaches the production of antibodies from known polypeptides, wherein the antibody can have predetermined specificity and in addition can be of a single specificity (i.e., monoclonal), and that antibodies made against a predetermined peptide are useful in studying the protein conformation of the intact protein from which the immunizing peptide was cleaved. The Examiner also states that Harlow *et al.* teach that peptides of six residues in length will consistently elicit antibodies that bind to the original protein.

Thus, the Examiner concludes that it would have been prima facie obvious to one having ordinary skill in the art to use the amino acid sequence taught by Yamagami *et al.* to produce monoclonal and polyclonal antibodies with a predetermined specificity as taught by Lerner with the expectation that these antibodies made against proteins with sequence identity to SEQ ID NO: 2 would be useful in understanding the conformational changes the receptor undergoes during activation by a natural ligand.

Applicants respectfully traverse this rejection. Yamagami *et al.* teach the cDNA cloning and functional expression of human MCP-1RB (CCR2B) (see page 1161, lines 11-16), which is an entirely different receptor from the CCR3 of the instant application. Thus, Yamagami *et al.*

do not teach or suggest an antibody or antigen binding fragment thereof which binds to a mammalian CCR3 protein or portion thereof. Yamagami *et al.* also do not teach or suggest an antibody or antigen binding fragment thereof which has binding specificity for mammalian CCR3 or portion thereof, which antibody or fragment inhibits binding of a ligand to the receptor and inhibits function associated with binding of the ligand to the receptor.

Lerner and Harlow *et al.* do not provide any teachings or suggestions related to CCR3, but rather provide generic teachings related to the production of antibodies in general. Thus, neither Lerner nor Harlow *et al.* teach or suggest an antibody or antigen binding fragment thereof which specifically binds to a naturally-occurring mammalian CCR3 protein, or an antibody or antigen binding fragment thereof which has binding specificity for naturally-occurring mammalian CCR3, which antibody or fragment inhibits binding of a ligand to the receptor and inhibits function associated with binding of the ligand to the receptor.

Applicants note that the stretch of 10 amino acids which the Examiner has identified as being identical with a portion of the amino acid sequence depicted in SEQ ID NO: 2 of the present application is an amino acid motif (DRYLAIVHA) which is highly conserved among C-C and C-X-C chemokine receptors (Specification, page 14, line 33, through page 15, line 3). Thus, an antibody which binds to this peptide sequence is likely to cross-react with a broad range of C-C and C-X-C chemokine receptors and will not specifically bind to CCR3 in accordance with Applicants' claimed invention. Thus, even if the combination of the references were properly made, it would not result in the claimed invention.

In view of the foregoing, it is clear that neither requirement needed to establish the obviousness of the claimed invention in light of the cited references under In re Vaeck has been met. Thus, the cited references do not render the claimed invention obvious. Reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (781) 861-6240.

Respectfully submitted,

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